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PATENT & TRADEMARK OFFICE

DECLARATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: PRASAD K. DESPANDE et al. Group: 1625

Serial No: 10/749,932

Examiner: Charanjit AULAKH

Filed: December 31, 2003

For: BENZOQUINOLIZINE-2-CARBOXYLIC ACID ARGININE SALT TETRAHYDRATE

Attorney docket: U 014681-4

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Mahesh V Patel, a citizen of India declare the following:

That the polymorph decides the aqueous solubility. For example, polymorph that have more aqueous solubility is thermodynamically less stable form and the polymorph where hydrogen bonding and Vander Waal forces are fully satisfied is more crystalline form and hence less soluble in water. Less stable polymorph, therefore, has more aqueous solubility (Ref. Drug and The Pharmaceutical Sciences, Vol. 45, Marcel Dekker, Inc., New York . Basel, Chapter 5, Generation of Polymorphs…., pp 190-191). If such a less stable polymorph is used in aqueous solution it tends to crystallise upon standing, thereby resulting precipitation in aqueous solution indicative of more stable polymorph formation. The use of more stable polymorph is therefore important for solution administration. The tetrahydrate form of the invention is more stable form where crystallinity is more than previously reported forms. It is incorrect that crystalline form lose their identity once dissolved in solution, as it is reported in the literature that one polymorph has more bioavailability than the other, for example, Erythromycin base exists in anhydrate, dihydrate and amorphous form but anhydrate and dihydrate absorb faster than amorphous. Similar case is reported for Chloramphenicol palmitate where Form B is orally more available than Form A. (Ref. Drug and The Pharmaceutical Sciences, Vol. 45, Marcel Dekker, Inc., New York . Basel, Chapter 7, Effects of Polymorphism…., pp 323-324).

We further declare that the solid composition such as tablets requires particular bulk density and particle size can be provided by simply changing polymorphs or hydrate. Additionally, when lesser hydrate is processed for making dough or granulation in water, a prerequisite for tablet preparation purpose, it is likely that the lesser hydrate may go to more stable tetrahydrate form. Whereas tetrahydrate form being last hydrate it will retain its identity as a tetrahydrate.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Signed this 4th day of August 2005

Patel M.V.

Mahesh V Patel

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Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids

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melting form is obtained. Thus the lower melting polymorph could be converted to the higher melting polymorph by recrystallizing from xylene (boiling point 137–140°C).

To understand how temperature influences the composition of crystals that form, it is useful to examine typical solubility–temperature diagrams for substances exhibiting monotropic and enantiotropic behavior [15]. In Fig. 1a, Form II, having the lower solubility, is more stable than Form I. These two noninterchangeable polymorphs are monotropic over the entire temperature range shown. For indomethacin, such a relationship exists between Forms I and II, and between Forms II and III.

In Fig. 1b, Form II is stable at temperatures below the transition temperature T_t, and Form I is stable above T_t. At the transition temperature the two forms have the same solubility, and reversible transformation between enantiotropic Forms I and II can be achieved by temperature manipulation. The relative solubility of two polymorphs is a

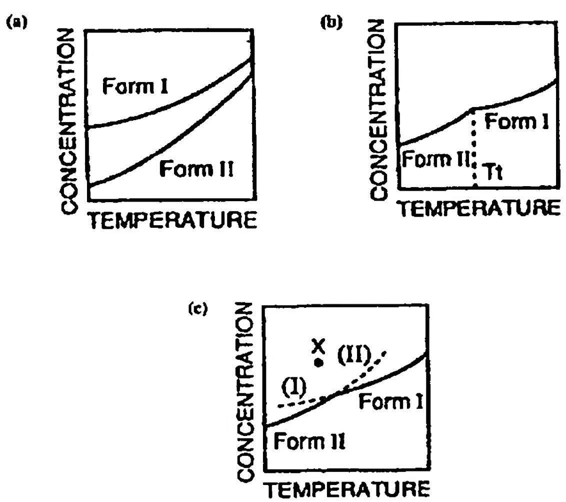

Fig. 1 Solubility curves exhibiting (a) monotropy, (b) enantiotropy, and (c) enantiotropy with metastable phases. (Reprinted with permission of the copyright holder [15].)

convenient measure of their relative free energies. The polymorph having the lower solubility is the more thermodynamically stable form, i.e., the form with the lower free energy at the temperature of the solubility measurement. At room temperature, carbamazepine Form I (m.p. 189°C) is more soluble than is Form III (m.p. 174°C), so the form with the higher melting point is more soluble. The polymorphs are enantiotropic with respect to each other [16].

There are situations in which kinetic factors can for a time override thermodynamic considerations. Figure 1c depicts the intervention of metastable phases (the broken line extensions to the two solubility curves). If a solution of composition and temperature represented by point X (supersaturated with respect to both I and II) is allowed to crystallize, it would not be unusual if the metastable Form I crystallized out first even though the temperature would suggest that Form II would be the more stable (i.e., less soluble) form. This is an extension of Ostwald's law of stages [17], which states that "when leaving an unstable state, a system does not seek out the most stable state, rather the nearest metastable state which can be reached with loss of free energy." This form then transforms to the next most soluble form through a process of dissolution and crystallization. Crystallization of Form I when Form II is more stable would be expected if Form I had the faster nucleation and/or crystal growth rate. However, if the crystals of Form I were kept in contact with the mother liquor, transformation could occur as the more soluble Form I crystals dissolve and the less soluble Form II crystals nucleate and grow. For crystals that exhibit this type of behavior, it is important to isolate the metastable crystals from the solvent by rapid filtration so that phase transformation will not occur.

In the general case, if there are any other polymorphic forms with solubilities below that of Form II, the above-described process will continue between each successive pair of forms until the system finally contains only the most stable (the least soluble) form. The implication of this hypothesis is that, by controlling supersaturation and by harvesting crystals at an appropriate time, it should be possible to isolate the different polymorphic forms. Furthermore, the theory predicts that at equilibrium the product of any crystallization experiment must be the stable form, regardless of the solvent system. It is apparent, however,

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Effects of Polymorphism and Solid-State Solvation on Solubility and Dissolution Rate

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Chloramphenicol palmitate has been shown to exist in four crystal odifications, and the effect of two of these on the degree of drug sorption has been compared [102]. After oral ingestion of Forms A d B, the highest mean blood levels were obtained with suspensions ntaining only Form B. In mixed dosage forms, the blood levels of e drug were found to bear an inverse relationship with the fraction Form A. This finding explained the previous report, which noted at a particular suspension formulation of chloramphenicol palmitate hibited an unsatisfactory therapeutic effect [103]. A study of various mmercial products indicated that the polymorphic state of the drug in is formulation was uncontrolled, consisting of mixtures of the active lymorph B and the inactive polymorph A.

Sulfamethoxydiazine has been shown to exist in a number of lymorphic forms, which exhibit different equilibrium solubilities and ssolution rates [104]. Form II, the polymorph with the greater thermo-namic activity, was found to yield higher blood concentrations than rm III which is stable in water [105]. This relationship is illustrated Fig. 11. Although the urinary excretion rates during the absorption ase confirmed the different drug absorption of the two forms as previ-usly observed, the extent of absorption (as indicated by 72-hour excre-on data) of the two forms was ultimately shown to be equivalent [106].

Fluprednisolone has been shown to exist in seven different solid ases, of which six were crystalline and one was amorphous [107]. f the crystalline phases, three were anhydrous, two were monohy-ates, and one was a *tert*-butylamine solvate. The in vitro dissolution te of the six crystalline phases of fluprednisolone were determined id compared with in vivo dissolution rates derived from pellet im-ants in rats [108]. The agreement between the in vitro and in vivo ssolution rates was found to be quite good, but the correlation with imal weight loss and adrenal gland atrophy was only fair. These re-ilts can be interpreted to indicate that, for fluprednisolone, differences dissolution rates of the drug did not lead to measurable biological fferences.

Erythromycin base is reported to exist in a number of structural rms, including an anhydrate, a dihydrate, and an amorphous form 09, 110]. The commercially available product appears to be a par-ally crystalline material, containing a significant amount of amor-

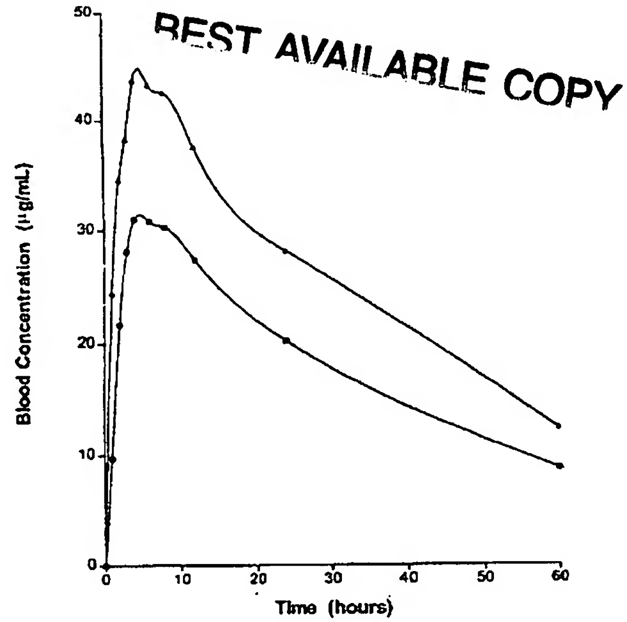

Fig. 11. Mean concentrations of sulfamethoxydiazine in blood as influenced by the polymorphic form of the drug substance. Shown are the profiles of Form II (-▲-) and Form III (-■-). (The figure has been adapted from data provided in Ref. 105.)

phous drug [111]. From studies conducted in healthy volunteers, it was learned that the anhydrate and dihydrate phases were absorbed faster and more completely than was either the amorphous form or the commercially available form [112]. These observations were reflected in the two pharmacokinetic parameters (C_{max} and AUC).

Azlocillin sodium can be obtained either as a crystalline form or as an amorphous form, depending on the solvent and method used for its isolation [113]. The antibacterial activity of this agent was tested against a large number of reference strains, and, in most cases, the crystalline form exhibited less antibacterial activity than did the amorphous form. Interestingly, several of the tested microorganisms also proved to be resistant to the crystalline form.